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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,687	10/02/2003	Mark T. Bilodeau	20721YCA	9784

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,687	BILODEAU ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-15,17-23,26-33,40 and 43-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5-9* is/are allowed.

6)☒ Claim(s) *1-4,10,12-15,17-23,26-33,40 and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12292003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 12-15, 17-23, 26-33, 40 and 43-47 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 22, 43 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, does not reasonably provide enablement for a method of treating age-related macular degeneration; a method of treating tissue damage to bacterial meningitis; or a method of treating cancer in combination with gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims are drawn to "a method treating cancer ... in combination with gene therapy"; "a method of treating age related macular degeneration"; "a method of treating tissue damage due to bacterial meningitis". Test assays and procedures are provided in the specification in pages 55-61 related to VEGF receptor kinase, FLT-1 and FLT-3 kinase inhibition, and it is concluded that the compounds of the invention "were found to have inhibitory activity" (see page 55), however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The provided kinase inhibitory activity relates to the corresponding diseases and there is nothing on the record how this links to all of the diseases of the instant claims, such that a reasonable extrapolation could be made by one skilled in the art regarding the therapeutic activity of the instantly claimed compounds. The disorders encompassed by the instant claims include cancers of all types, age-related macular degeneration and tissue damage due to bacterial meningitis, some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

'Cancer' generally refers to anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. No compound has ever been found to treat cancers of all types generally. Since this assertion is

contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36. The claims include 'treating **all types of cancer** by administering the compound in combination with gene therapy' and a state of the art reference indicates that 'further evolutions in vector development, thorough understanding of tumor and cellular immunology, and the expansion of therapies that restrict angiogenesis will be necessary for advancement of the course of cancer gene therapy' (see Hall et al., cited in IDS).

The claims recite the use of the instantly claimed compounds in 'treating age-related macular degeneration'. A state of the art reference, Roodhooft (PubMed Abstract enclosed) provides that 'there is no efficacious treatment for age-related macular degeneration'.

The claims include 'treating tissue damage due to bacterial meningitis' and a state of the art reference, Matsuyama et al. (cited in IDS) states that "detailed roles of VEGF in tuberculosis

meningitis still remain unresolved" (see page 79). Another publication by van der Flier et al. (cited in IDS) regarding VEGF in bacterial meningitis, concludes that 'further research is required to elucidate the exact role of VEGF in this disease'.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that "The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 10, 12-15, 17-23, 26-33, 40 and 43-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, in the definition of R^6, the numbers "4) 5) 6) 7) 8)" remain. Since there are only four groups under the definition of R^6, the groups should appropriately renumbered. Further, following the last group 'heterocyclyl', the term -- wherein -- should be inserted before 'said phenyl ....'. The discrepancy is found in claim 2 also.
2. Claim 4 recites the limitation "R^2 is $O_r(C_1$-$C_6)$alkyl" in lines 1-2. There is insufficient antecedent basis for this limitation in claim 1 on which claim 4 is dependent (via claims 3 and 2). Claim 1 recites that "R^2 is $(C=O)_rO_s(C_1$-$C_{10})$alkyl". While r and s both can be 0 or 1, consistent subscripts along with the groups should be maintained throughout the claims. The recitation in claim 4 may be considered proper if amended as -- $O_s(C_1$-$C_6)$alkyl --.

Allowable Subject Matter

Claims 5-9 are allowed. Claims 1-10, 12-15, 17-18, 20-21, 23, 26-33, 40, and 44-46 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112,

2nd paragraph, set forth in this Office action. The closest reference of record, WO 00/39101 teaches substituted pyrimidine compounds having a 4-methyl-thiazol-2-yl attached to the 4-position of the pyrimidine through –NH- group. The instant claims require that the substituent at the 4-position of the thiazolyl ring (R^6) is selected from phenyl, CN, halogen or heterocyclyl. The reference does not teach or fairly suggest such compounds.

Receipt is acknowledged of the Information Disclosure Statement filed on December 29, 2003 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

October 31, 2005